REMARKS

Applicant respectfully requests reconsideration of the present application in view of the reasons that follow.

I. Status of Claims

With this submission, no claims are amended, canceled or newly added. Hence, upon entry of this paper, claims 5, 8-12, and 15 will remain pending and under active consideration.

II. Rejection Under 35 USC § 103

The Office rejects claims 5, 8-12 and under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ahern et al. (Europ. J. of Pharacol., 2000) ("Ahern") in view of MacDonald et al. (Diabetes, 2002) ("MacDonald") and Nauck et al., (Diabetes Care, 1998) ("Nauck"). (Office Action, page 2) Applicant respectfully traverses this rejection. The Office rejects claim 15 as allegedly being unpatentable over Ahern, MacDonald, and Nauck and in further view of Deacon et al. (Expert Opin. Investig. Drugs, 2004) ("Deacon"). Applicant respectfully traverses this rejection.

A. Current Obviousness Standard

The Supreme Court recently reaffirmed the Graham factors for determining obviousness in *KSR Int'l Co. v. Teleflex Inc.* (No. 04-1350) (U.S., April 30, 2007). The Graham factors, as outlined by the Supreme Court in *Graham et al. v. John Deere Co. of Kansas City et al.*, 383 U.S. 1 (1966), are: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the claimed invention and the prior art; 3) resolving the level of ordinary skill in the pertinent art; and 4) evaluating evidence of secondary consideration. The Supreme Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a), and held that the proper inquiry for determining obviousness is whether the improvement is more than the predictable use of prior art elements according to their established functions. The Court noted that it is "important to identify a reason that would

have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed, and specifically stated:

> Often, it will be necessary . . . to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was ***an apparent reason to combine the known elements in the fashion claimed*** by the patent at issue. To facilitate review, this analysis should be made explicit.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 418 (2007) (emphasis added). As discussed below, the cited art cannot render the claimed invention obvious.

B. Ahren, MacDonald and Nauck Do Not Render the Invention Obvious

The Office asserts that Ahern in view of MacDonald and Nauck render claims 5, 8-12 obvious. In an earlier action, the Office agreed that Ahren and Nauck alone did not render the invention obvious (see Statement of Substance of Interview, Nov. 17, 2009). In summary, Applicant included in the claims an active positive step of "testing if said mammal can no longer close an ATP-sensitive K+ channel due to stimulation by a sulfonylurea receptor 1-binding compound." Applicant submits that the addition of the MacDonald reference does not cure the previously traversed obviousness rejection because, as the Office admits, "MacDonald does not teach a method of treating diabetes with sulfonyl secondary failure or a method of promoting insulin secretion in a diabetic patient in need thereof with sulfonylurea secondary failure by (a) testing if said mammal can no longer close an ATP-sensitive K+ channel due to stimulation by a sulfonylurea receptor 1-binding compound, and (b) administering to said mammal an effective amount of a dipeptidyl peptidase IV inhibitor." (Office Action, Dec. 27, 2010; page 3)

1. Ahren, MacDonald and/or Nauck do Not Teach All of the Steps in the Claimed Invention

The cited prior art does not teach all steps in the claimed invention. The claims include the step of "testing if said mammal can no longer close an ATP-sensitive K+ channel due to stimulation by a sulfonylurea receptor 1-binding compound." None of the references teaches how the dipeptidyl peptidase IV inhibitor is used. In fact, none of the references

disclose testing if a mammal can no longer close an ATP-sensitive K+ channel due to stimulation by a sulfonylurea receptor 1-binding compound, nor do they suggest administering to said mammal an effective amount of a dipeptidyl peptidase IV inhibitor. While Nauck discusses sulfonylurea secondary failure, it notes that "[t]his purely clinical classification may appear a little imprecise, but no clearer criteria are available at the present." (page 1929; col. 3; paragraph 2). Furthermore, Nauck states that it "does not make a direct comparison between GLP-1 effect in between normal versus type 2 diabetic patients or between different stages of type 2 diabetes." (page 1929; col. 2; first paragraph). Therefore, the step of "testing if said mammal can no longer close an ATP-sensitive K+ channel due to stimulation by a sulfonylurea receptor 1-binding compound" is not included in the prior art.

2. No Motivation to Combine Ahren with Nauck and MacDonald

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. KSR. (MPEP 2143.01)

As previously mentioned in the Office action response dated October 21, 2009, DPP-IV was originally identified as a protein on lymphocytes, and associated with white blood cells in the immune system.[1] In fact, DPP-IV was initially thought to be involved in severe combined immunodeficiency disease. This led some researchers to argue that inhibiting DPP-IV might impair the immune system.[2] It was only later found on many different types of tissue, including the kidneys, lungs, liver, intestines, pancreas, blood vessels and brain. Additionally, DPP-IV has been shown to have a role in cancer.[3]

One of skill in the art would not know how to combine the DPP-IV inhibitor of Ahren with the sulfonylurea secondary failure function of GLP-1 disclosed in Nauck. This is because DPP-IV is found on many different cell types and has several different functions associated with several different disease types. The Office states that "the glucose threshold

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[1] Kameoka, J. et al. "Direct association of adenosine deaminase with a T-Cell activation antigen, CD26" Science1:466-469 (1993).

[2] http://www.diabetesselfmanagement.com/Articles/Diabetes-Research/dpp-4-inhibitors/All/ visited May 27, 2011.

[3] Pro, B. and Dang, N.H. "CD26/dipeptidyl peptidase IV and its role in cancer" Histol. Histopathol. 19(4): 1345-51 (2004); Havre, P.A. et. al. "The role of CD26/dipeptidyl peptidase IV in cancer" Front Biosci. 13:1634-45 (2008).

for insulin secretion is the same for patients with sulfonylurea secondary failure as taught by Nauck." (Office Action, Dec. 27, 2010; page 4) However, Nauck states explicitly that it "does not make a direct comparison between GLP-1 effect in between normal versus type 2 diabetic patients or between different stages of type 2 diabetes." (page 1929; col. 2; first paragraph). Ahren and MacDonald do not reference or consider sulfonylurea secondary failure of the present invention, and therefore lack of motivation to combine with Nauck, which specifically disclaims other types of diabetic patients.

Therefore, neither Ahren, MacDonald nor Nauck disclose or suggest the method of treating diabetes with sulfonylurea secondary failure, or of promoting insulin secretion in a diabetic patient with sulfonylurea secondary failure, by administering a dipeptidyl peptidase IV inhibitor to a mammal or a patient who can no longer close an ATP-sensitive K+ channel due to stimulation by a sulfonylurea receptor 1-binding compound.

3. The Claimed Invention Yields Unexpected Results

When one considers the obviousness of a combination of known elements, the operative question is "whether the improvement [in combining elements found in the prior art] is more than the predictable use of [the] elements according to their established functions." MPEP § 2141(I), citing *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007). "While obviousness does not require absolute predictability, *at least some degree of predictability is required.*" MPEP § 2143.02(II) (emphasis added). Evidence of unexpected results must be weighed against evidence supporting prima facie obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA178) (See also MPEP 716.02(c))

The advantages of the claimed invention would not naturally flow from the suggestions of Ahren, Nauck and/or MacDonald because the use of a DPP-IV inhibitor yields unexpected results. Specifically, the use of DPP-IV for the treatment of diabetes with sufonylurea secondary failure produces lower side effects as compared to treatment with a GLP-1 analogue. In contrast, GLP-1 analogues cause side effects such as vascular complication, hypoglycemia, and vomiting. (Specification page 4, see also *Amori et al.* JAMA 298: 194-206 (2007) at 203) Additionally, neither Ahren, Nauck nor MacDonald suggest or disclose a method of treating diabetes with sulfonylurea secondary failure, or of

promoting insulin secretion in a diabetic patient with sulfonylurea secondary failure by administering a dipeptidyl peptidase IV inhibitor.

Thus, there would have been no reason for one of skill in the art, in view of Ahren, Nauck and MacDonald, to arrive at Applicant's claimed methods of treating diabetes with sulfonylurea secondary failure or of promoting insulin secretion in a diabetic patient with sulfonylurea secondary failure. Accordingly, the methods as presently claimed would not have been obvious in light of Ahren, Nauck and MacDonald.

In sum, the prior art cited by the Examiner in the obviousness rejection cannot be evaluated in isolation, but must now be considered in light of the objective evidence presented bearing on obviousness. The evidence presented strongly supports a case of non-obviousness. For at least the reasons presented above, applicant believes that the rejection of claims 5 and 8-12 under 35 U.S.C. § 103 has been overcome. Accordingly, Applicant respectfully requests that the Examiner withdraw this rejection.

C. Claim 15 is Non-Obvious over Ahern, MacDonald, and Nauck and in further view of Deacon

With regard to claim 15, Applicant notes that the citation of Deacon, which is alleged to teach the specific compound claimed in claim 15, does not cure the inability of Ahern, MacDonald, and Nauck to render obvious the subject matter of the independent claims. Thus the combination of Ahern, MacDonald, Nauck, and Deacon likewise fails to teach or suggest the subject matter of claim 15.

For at least these reasons, Applicant respectfully requests reconsideration and withdrawal of the rejection.

CONCLUSION

Based on the foregoing remarks, Applicant respectfully requests that the Examiner reconsider all rejections and that they be withdrawn. Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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